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Serum Vasopressin (AVP) Levels in Polyuric Brain-Dead Organ Donors*

M. Hohenegger[1], M. Vermes[1], W. Mauritz[2], G. Redl[2], P. Sporn[2], and P. Eiselsberg[1]

[1]Institute of General and Experimental Pathology and [2]First Department of Intensive Care Medicine, Clinic of Anaesthesiology, University of Vienna, Vienna, Austria

Summary. Hydromineral metabolism and serum arginine-vasopressin (AVP) levels were investigated in 11 patients who sustained brain death. They showed various degrees of polyuria with low osmolality and low fractional sodium excretion. Urine osmolality was always below that of serum, and AVP levels were between 1.3 and 50.0 pg/ml vs 0.7–8.0 pg/ml in ten normal subjects. Thus central diabetes insipidus was excluded. A renal mechanism inducing water diuresis has to be assumed. The type of renal lesion, however, remains unclear.

Key words: Brain death – Diabetes insipidus – Serum arginine-vasopressin (AVP)

Introduction

Brain-dead organ donors often exhibit massive polyuria (Black 1978; Draxler et al. 1977; Mollaret and Goulon 1959; Outwater and Rackoff 1984; Schneider et al. 1969). As the pathogenesis is not clear we measured serum arginine – vasopressin (AVP) levels in these organ donors. In this way we hoped to distinguish between central diabetes insipidus and a renal mechanism. This question may be also of practical importance in deciding optimal fluid and electrolyte replacement after brain death.

Materials and Methods

Eleven patients, aged between 6 and 48 years, were investigated. All of them except two (no. 3: status asthmaticus; no. 5: intracranial aneurysm) suffered from severe brain trauma. All patients were under controlled ventilation.

During the polyuric phases the therapy consisted of perfusions containing 75 mmol sodium chloride and 25 g fructose/l. For stabilizing potassium and acid – base homeostasis 20 mmol potassium bicarbonate/l urine excreted were additionally applied. If serum osmolality was above 310 mosmol/kg a 5% fructose solution without sodium chloride was given. The perfusions contained dopamine (2 μg/kg body weight/min); no other drugs were given. Brain death occurred between 10 and 36 h after trauma or onset of the acute illness. For this diagnosis the criteria as described by Black (1978) and Pendl (1986) were employed: non-reacting coma, absence of cephalic reflexes, absence of spontaneous breathing and isoelectric EEG. Six hours after the onset and persistence of these symptoms the organs were removed for transplantation.

Urine was collected during polyuria in periods of 1–4 h. Between these periods venous blood samples were taken. In the serum and urine osmolality, urea, creatinine, sodium, potassium and glucose were measured as described previously (Draxler et al. 1977; Hohenegger et al. 1974; Om and Hohenegger 1980).

AVP was determined for the first time in blood samples obtained at least 2 h after the onset of brain death. In patients 3, 4, 8, 9, 10 and 11, immediately after the first blood sampling for AVP measurement 5 IU AVP (Parke and Davis) was injected intravenously. Fifteen minutes later a further venous blood sample was taken for measuring serum AVP and serum osmolality. After the injection of AVP a new urine collection period was started.

On the basis of osmolality, creatinine and sodium concentration in serum and urine creatinine-, osmolar-, free water clearance as well as fractional sodium excretion were calculated.

Measurement of Serum AVP. Venous blood was collected under ice and immediately centrifuged at 4°C. Measurements were performed by radioimmunoassay. The sera were extracted with cooled acetone and petroleum ether (Husain et al.1973; Robertson et al. 1973) and were then evaporated under nitrogen at room temperature. The samples were stored at −20°C for a few weeks until final measurements were carried out. From each sample 2 × 1 ml serum were extracted and analysed in duplicate. The initial volume was restord with 0.1 M phosphate buffer, pH7.4. As an antibody anti-AVP rabbit serum (Ferring, Kiel, FRG) was used, final dilution 1:250,000. As a

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Offprint requests to: M. Hohenegger, Laxenburgerstrasse 39, A-1100 Wien, Austria

Table 1. Clinical data of 11 brain-dead organ donors

Patients		Age (years)	P_{osm}[a] (mosmol/kg)	U_{osm} (mosmol/kg)		Urine volume[a] (ml/min)	C_{H_2O}[a] (ml/min)	C_{cr}[a] (ml/min)	Plasma AVP[c] (pg/ml)
No.	Sex (M, F)								
1.	M	6	280	220[a]		6.3	+ 1.4	71	2.0
2.	M	21	331	213[a]		2.5	+ 1.0	43	6.0
3.	M	42	301	50[a]	69[b]	17.1	+ 14.2	95	11.0
4.	M	35	318	101[a]	100[b]	11.7	+ 8.0	145	8.0
5.	F	40	298	122[a]		20.8	+ 12.3	208	21.0
6.	M	32	290	178[a]		18.8	+ 7.3	180	50.0
7.	M	22	327	167[a]		20.8	+ 10.2		21.0
8.	F	36	322	274[a]	298[b]	11.6	+ 1.7	141	18.0
9.	M	48	343	106[a]	130[b]	8.3	+ 5.7	108	1.3
10.	M	16	280	87[a]	272[b]	22.2	+ 15.1	155	9.0
11.	M	13	315	57[a]	53[b]	11.3	+ 9.3	111	4.4
Mean		28.3	309.5	143.2	153.7	13.8	+ 7.8	126	13.8
SD		13.4	21.2	72.5	105.4	6.6	+ 5.0	50	13.9

[a] During 1–4 h urine collecting period before AVP measurement
[b] During 1–4 h collecting period following intravenous injection of 5 IU AVP
[c] Before injection of exogenous AVP

tracer ^{125}I-AVP (New England Nuclear), 2 pg per test tube, was added (corresponding to about 4000 cpm). Precipitation was accomplished with NN–Immunosorbent (Biomedica, Vienna, Austria). AVP standards were obtained from Ferring, Kiel. Cross-reactivity with oxytocin was less than 0.1%; the recovery rate was 65%–70% in the range of 1 pg AVP/ml and about 85% above 5 pg/ml. The results were not corrected for recovery rates.

Employing this method we found serum AVP levels between 0.7 and 0.8 pg/ml in 10 normal persons who had no abnormalities of hydromineral metabolism.

Results

The main results are presented in Table 1. Polyuria was excessive in cases 5, 6, 7, and 10. Urine osmolality was always below that of serum; in cases 3, 10, and 11 it was below 100 mosmol/kg. In each case free water clearance was positive; creatinine clearance was in the upper normal range in most cases; only in patient 2 was it reduced. Average serum osmolality was rather elevated.

Serum AVP levels were between 1.3 and 50 pg/ml and were not correlated with serum osmolality (correlation coefficient $r = -0.26$, $P > 0.05$). As can be seen in Table 1 there was only a small effect of exogenous AVP on urine osmolality. In no case did urine osmolality exceed that of serum following intravenous injection of AVP. Fifteen minutes after AVP injection serum levels of AVP between 60 and 300 pg/ml were measured.

Additional results, not indicated in the table were: serum sodium concentrations of 150 ± 8.6 mmol/l, corresponding well with relative high serum osmolality; normal serum potassium of 4.3 ± 0.7 mmol/l; low fractional sodium excretion rates of $1.08 \pm 0.9\%$ of the filtered load (values indicate means $\pm$ SD). In the urines glucose could not be detected by employing Amex test tapes, except for traces in case 6.

Discussion

In all patients AVP serum levels were within or above the normal range. The response of urine flow and urine osmolality to exogenous AVP was lacking or inadequate. Consequently central diabetes insipidus can be ruled out. A renal mechanism has to be assumed. First, renal diabetes insipidus with total or partial unresponsiveness of the distal nephron to AVP seems possible. As the organ donors received large quantities of infusions washout of the renal countercurrent system has also to be considered. In this case water diuresis with lack of response to AVP may occur, as is well known from studies in psychogenic polydipsia (Hariprasad et al. 1980; Smith and Clark 1980; Wedeen 1961; Zerbe and Robertson 1981). It is generally advised that one should differentiate such cases from other forms of diabetes insipidus by inducing water restriction. This procedure should then normalize polyuria and concentration ability within several hours. In brain-dead organ donors this

method cannot be applied because there is a critical state of cardiovascular function, and removal of organs for transplantation is performed with 6 h after diagnosis of brain death.

The rather high levels of serum AVP and osmolality do not support the washout mechanism. In water-loaded patients with psychogenic diabetes insipidus generally low serum osmolality and low serum AVP as a consequence of volume expansion, have been reported (Zerbe and Robinson 1981). The type of diuresis in our brain-dead organ donors is essentially water diuresis, as on the average urine osmolality was only 143 mosmol/kg and fractional sodium excretion only 1.08% of the filtered load. In osmotic diuresis much higher fractional sodium excretion and urine osmolality above that of serum is typical (Rapoport et al. 1949; Lang 1987). Even in our cases with relative high urine osmolality (but still below serum osmolality) only one specimen contained traces of glucose. Thus glucose plays no role in urine osmolality in these cases. Probably fructosuria is present in some patients, moderately increasing the urine osmolality to values slightly below serum osmolality. This remains, however, to be demonstrated by direct measurements.

Dopamine was certainly not an essential factor for polyuria in brain-dead organ donors because this substance also increases absolute and fractional sodium excretion. Furthermore, polyuria is not always correlated with the onset and withdrawal of dopamine application (Draxler et al. 1977; Outwater and Rackoff 1984). In the state of brain death secretion of AVP by the posterior hypophysis is rather unexpected. Thus, the relatively high serum levels need further study. One explanation might be that there is some residual cerebral blood flow in brain-dead subjects, still able to transport AVP to the peripheral blood. Such residual flow has been demonstrated by Angstwurm and Frick (1980), Schneider et al. (1969) and Shalit et al. (1970) in several patients with the typical clinical symptoms of brain death including isoelectric EEG.

Reduced degradation of serum AVP in brain death might be another explanation, but this remains to be proven by direct measurements.

References

Angstwurm H, Frick E (1980) Neurologische Diagnose and Dokumentation des "Hirntodes" potentieller Organspender. Münch Med Wochenschr 122:1371–1373

Black P McL (1978) Brain death. N Engl J Med 299:338–344

Draxler V, Krenn J, Sporn P, Steinbereithner K, Watzek C, Hohenegger M, Pinggera W, Stummvoll H, Wolf A (1977) Verhalten renaler and zirkulatorischer Funktionsparameter bei Kadavernierenspender unter Dopamin. Klin Wochenschr 55:545–552

Hariprasad MK, Eisinger RP, Nadler IM, Padmanabham CS, Nidus BD (1980) Hyponatremia in psychogenic polydipsia. Arch Inter Med 140:1639–1642

Hohenegger M, Brechtelsbauer H, Finsterer U, Prucksunand P (1974) Effects of inhibitors of fatty acid oxidation on renal function. Pflügers Arch 131:231–240

Husain MK, Fernando N, Shapiro M, Kagan A, Glick SM (1973) Radioimmunoessay of arginine vasopressin in human plasma. J Clin Endocrinol Metab 37:616–625

Lang F (1987) Osmotic diuresis. Renal Physiol 10:160–173

Mollaret P, Goulon M (1959) Le coma depassé. Rev Neurol (Paris) 101:3–15

Om P, Hohenegger M (1980) Energy metabolism in acute uremic rats. Nephron 25:249–253

Outwater K, Rackoff M (1984) Diabetes insipidus accompanying brain death in children. Neurology 34:1243–1246

Pendl G (1986) Der Hirntod. Springer, Vienna New York

Rapoport S, Brodsky WA, West CD, Mackler B (1949) Urine flow and excretion of solutes during osmotic diuresis in hydropenic man. Am J Physiol 156:433–442

Robertson GL, Mahr EA, Athar S, Sinha T (1973) Development and clinical application of a new method for the radioimmunoessay of arginine vasopressin in human plasma. J Clin Invest 52:2340–2352

Schneider H, Masshoff W, Neuhaus GA (1969) Klinische und morphologische Aspekte des Hirntodes. Klin Wochenschr 16:844–859

Shalit MN, Beller AJ, Feinsod M (1970) The blood flow and oxygen consumption of the dying brain. Neurology 20: 740–748

Smith WO, Clark ML (1980) Self-induced water intoxication in schizophrenic patients. Am J Psychiatry 137:1055–1060

Wedeen R (1961) Prolonged functional depression of antidiuretic mechanism in psychogenic polydipsia simulating primary diabetes insipidus. Ann Inter Med 54:805–809

Zerbe RL, Robertson GL (1981) Comparison of plasma vasopressin measurements with a standard indirect test in the differential diagnosis of polyuria. N Engl J Med 305:1539–1546

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